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UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/853,427	Applicant(s) Mullin et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 20, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *3, 4, and 7-9* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3, 4, and 7-9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment, Declaration under 37 CFR 1.132, and the Declaration filed October 20, 2003 in response to the Office Action of June 16, 2003 are all acknowledged and have been entered. Previously pending claims 1-2, 5, 10-12 have been canceled, claims 3, 7 have been amended. Claims 3-4, 6-9 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection

3. The amendment filed October 20, 2003 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment of page 5, lines 12-20 from "are taken of histologically normal mucosa from the edge of the excised tissue alongside portions" to "are taken from histologically normal mucosa from the edge of the excised tissue alongside portions" alters the scope of the specification. No support for this amendment has been presented. Applicant is invited to point to the page and line number wherein support for this amendment can be found. Applicant is required to cancel the new matter in the response to this Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. Claims 3-4, 6-9 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing Barrett's esophageal condition in a patient comprising administering to said patient an appropriate amount of at least one signature carbohydrate wherein said patient does not have ulcerative disease of the gastrointestinal tract nor bleeding therefore, collecting urine and measuring levels of said signature carbohydrate wherein an increase in the urine levels of said at least one carbohydrate is indicative of Barrett's esophageal condition in said patient.

The specification teaches that cancerous epithelial tight junctions will allow for the diffusion of proteins and sugars from the lumen of the esophagus into the bloodstream. This can provide a non-invasive early warning to cancerous and precancerous inflammatory states in epithelial tissues (p. 2, lines 5-11). The specification further teaches methods for detection and analysis of sucrose leaking across gastroesophageal mucosa into the bloodstream (para bridging pages 5-6) and methods of comparing the detection with levels in normal controls. One cannot extrapolate the teaching of the specification to the enablement of the claims because although the specification teaches that not only precancerous but also cancerous epithelial tight junctions will allow for the diffusion of sugars from the lumen of the esophagus into the bloodstream, the specification does not teach how to differentiate between cancerous, precancerous inflammatory states other than Barretts esophageal condition and Barretts esophageal condition as claimed, simply by assaying for at least one signature carbohydrate in urine. Given the teachings of the

specification, it is clear that it would be expected that any or all cancerous or precancerous conditions of the esophagus would result in a finding of increased carbohydrate in urine. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the finding of increased urine levels of at least one carbohydrate in a patient is indicative of Barrett's esophageal condition in said patient, rather than indicative of some other cancerous or precancerous condition. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

5. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 3-4, 6-9 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for the claimed method for diagnosing Barretts esophageal condition comprising assaying urine for elevated levels of sucrose compared to normal control, does not reasonably provide enablement for the claimed method for diagnosing Barretts esophageal condition comprising assaying urine for at least one elevated signature carbohydrate/mannitol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for diagnosing Barretts esophageal condition comprising assaying urine for at least one elevated signature carbohydrate.

This means assay for any signature carbohydrate. The specification teaches that sucrose is an excellent marker for ulceration-type leakiness in the upper GI tract because it is normally completely broken down on the duodenal microvilli and is normally completely absent from the bloodstream. When there is a defect in the gastric barrier which would enable undegraded sucrose to diffuse into the bloodstream the sucrose it can be subsequently quantitated in blood and then in urine (p. 14, lines 17-25). The specification further teaches that mannitol, specifically claimed in claim 4, is useful for *in vitro* assay of TJ leakiness of DMH treated colon tissue samples, wherein transepithelial flux of mannitol was observed. Further, the specification teaches an *in vitro* assay for the determination of tight junction permeability using mannitol (p. 13, lines 6-12). It is noted that no other "signature" carbohydrates are taught in the specification. One cannot extrapolate the teachings of the specification to the scope of the claims because there is no teaching in the specification or the art of record that any carbohydrate other than sucrose will function as claimed. There is no teaching in the specification of any other carbohydrate that would be a "signature" carbohydrate. There is no teaching of sources of such carbohydrates or how to administer them so that they would function as claimed. Further, although sucrose is known as an excellent marker for esophageal TJ leakiness, and therefore would be expected to also be an appropriate marker for the claimed invention, given the newly submitted Mullin Declaration, the same can not be said for mannitol or any other carbohydrate since there is no teaching that mannitol or any other carbohydrate would diffuse into the bloodstream from an esophageal entry source and arrive in the urine in an undegraded state.

Although it is clear that mannitol is useful for *in vitro* assays wherein it is not subject to the *in vivo* environment, it appears from the information in the specification that it cannot be predicted that mannitol would function as claimed in a urine assay. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that any carbohydrate other than sucrose would function as claimed. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. Claims 3, 6-9 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 4, 6-9 are drawn to signature carbohydrates to be used in the method of diagnosing Barrett's esophageal conditions. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure,

other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a signature carbohydrate itself logically cannot adequately describe a method of using that signature carbohydrate.

Thus, the instant specification may provide an adequate written description of the signature carbohydrates to be used in the claimed assay, per Lilly by structurally describing a representative number of the signature carbohydrates to be used in the claimed assay or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the signature carbohydrates to be used in the claimed assay in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses sucrose as an excellent marker and discloses mannitol in a manner that makes it unclear whether it can be used as claimed, this does not provide a description of the signature carbohydrates to be used in the claimed assay that would satisfy the standard set out in Enzo.

The specification also fails to describe the signature carbohydrates to be used in the claimed assay by the test set out in Lilly. The specification describes only sucrose as an excellent marker and discloses mannitol in a manner that makes it unclear whether it can be used as claimed. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the signature carbohydrates to be used in the claimed assay that are required to practice the claimed invention. Since the specification fails to adequately describe the signature carbohydrates to be used in the claimed assay, it also fails to adequately describe the claimed assay.

7. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 8-9 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for the claimed method for the diagnosis of Barrett's esophageal condition further comprising assaying an esophageal mucosa of a patient for tight junction leakiness, does not reasonably provide enablement of the claimed diagnosis of Barrett's esophageal condition further comprising assaying an esophageal mucosa of a patient for tight junction leakiness wherein TJ leakiness is correlated with altered expression levels of a protein, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to the diagnosis of Barrett's esophageal condition comprising assaying an esophageal mucosa of a patient for tight junction leakiness wherein TJ leakiness is correlated with altered expression levels of a protein, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin. This includes altered expression level of any protein and altered expression either over or underexpression of said protein. The specification teaches that cancerous and precancerous epithelial tight junctions will allow for the diffusion of proteins and sugars from the lumen of the esophagus into the bloodstream. This can provide a non-invasive early warning to cancerous and precancerous inflammatory states in epithelial tissues (p. 2, lines 5-11). The specification suggests that the level of expression and the phosphorylation state of occludin can be tested in patients with Barrett's esophagus (para bridging pages 5-6) and compared to normal controls. It is noted that there is no teaching that there is any alteration in the level of expression or the phosphorylation state of occludin in esophagus of patients with Barrett's esophagus. The tight junction appears to be made up of occludin, which contains a binding site for ZO-1, and claudins in association with the actin cytoskeleton (p. 7, lines 14-19). Altered tight junction structure has been demonstrated in cancer (p. 8, line 13). In *in vitro* studies, it was found that neither the expression nor the localization of occludin is changed by treatment of epithelial cell sheets to TPA (a phorbol ester that is capable of causing transepithelial leakiness to salts in a renal epithelial cell line p. 9, lines 4-6).

However, this treatment led to decrease in occludin threonine phosphorylation and a down regulation of ZO-1 expression (p. 11 (p. 11, lines 1-17). Assay of biopsy tissue will enable determination of whether or not the occludin expression and/or phosphorylation state is altered in precancerous tissue of the esophagus as a correlate to changes in TJ permeability in the precancerous state (p. 15, lines 15-26). One cannot extrapolate the teaching of the specification to the scope of the claims because the findings drawn to alterations in protein phosphorylation and expression levels appears to be based on *in vitro*, cell culture data. There is no guidance on or exemplification of any correlation between the alterations in phosphorylation and expression seen in cells in culture, wherein said cells are in constant contact with high concentration levels of TPA which is a known carcinogenic agent, and the *in vivo* condition. The *in vitro* experimental data presented is clearly not drawn to assays of human subjects. In particular, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences

In Vitro). Further, although partly drawn to cancer cell line cell culture, the findings of Dermer (Bio/Technology, 1994, 12:320) are also relevant to the instant fact pattern. Dermer teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, there is any alteration in phosphorylation of occludin or that there is any altered expression level of any protein that is correlated with Barrett's esophageal condition. Again, although drawn to the cancer cell line art, the findings of the following are clearly relevant to the instantly claimed invention. . In particular, the artifactural nature of cell lines is well known in the art and it is not clear from the information in the specification or the art of record whether the alterations in expression of ZO-1 or phosphorylation of occludin is an artifact of the cell culture system of this particular epithelial cell line or whether this can be in any way related to the *in vivo* Barrett's esophageal condition cells. For example,

Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Thus, based on the cell culture data presented in the specification, in the absence of data provided from Barretts esophageal cells and normal controls, no one of skill in the art would believe it more likely than not that the claimed alterations in phosphorylation state and expression levels would be altered in the same way in the *in vivo* condition. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed alterations would be found in Barrett's esophageal condition *in vivo* as claimed. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 8 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 8 is drawn to the association of tight junction leakiness, indicative of Barrett's esophageal condition, which is correlated with altered expression levels of a protein. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a protein itself logically cannot adequately describe a method of using that protein.

Thus, the instant specification may provide an adequate written description of the association of tight junction leakiness, indicative of Barrett's esophageal condition, which is correlated with altered expression levels of a protein, per Lilly by structurally describing a representative number of the proteins with altered expression or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the association of tight junction leakiness, indicative of Barrett's esophageal condition, which is correlated with altered expression levels of a protein in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses that ZO-1 is downregulated in an *in vitro* assay of TPA induced tight junction leakiness, this does not provide a description of the association of tight junction leakiness, indicative of Barrett's esophageal condition, which is correlated with altered expression levels of a protein that would satisfy the standard set out in Enzo.

The specification also fails to describe the proteins whose expression levels are altered by the test set out in Lilly. The specification describes only that ZO-1 is downregulated in an *in vitro* assay of TPA induced tight junction leakiness. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to

the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the signature carbohydrates to be used in the claimed assay that are required to practice the claimed invention. Since the specification fails to adequately describe the signature carbohydrates to be used in the claimed assay, it also fails to adequately describe the claimed assay.

9. Claims 3-4, 6-9 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a method of diagnosing Barrett's esophageal condition comprising assaying patient urine for at least one signature carbohydrate has no clear support in the specification and the claims as originally filed. A review of the specification reveals support for precancerous and cancerous epithelial tight junctions allowing for the diffusion of proteins and sugars from the lumen of the esophagus into the bloodstream. This can provide a non-invasive early warning to cancerous and precancerous inflammatory states in epithelial tissues (p. 2, lines 5-11). Serum levels salivary amylase have important diagnostic predictive value for Barrett's esophageal condition (p. 3, lines 10-15). The invention relates to detecting leakage of signature carbohydrates from the epithelium into the bloodstream which serves as a basis for detecting both cancerous and precancerous conditions (p. 3, lines 21-25). The specification suggests that serum levels of a broad range of endoscopy patients, including those with Barrett's esophagus, be assayed for serum levels of salivary amylase (p. 5, lines 29-34 and page 14, lines 8-14). There is no specific reference in

the specification to a urine assay for any carbohydrate for the diagnosis of Barrett's esophageal condition. The only references in the specification drawn to diagnosis of Barrett's esophageal condition are drawn to serum assays of serum amylase. The subject matter claimed in claims 3-4, 6-9 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 3-4, 6-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-4, 6-9 are indefinite in the recitation of "signature" carbohydrate. The claims are confusing because although the specification states that sucrose and mannitol are signature carbohydrates, neither the claims nor the specification define the term "signature", which appears to be a relative term, and it is not possible to determine the metes and bounds of the claimed invention.

11. All other objections and rejections recited in the first action on the merits are withdrawn.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
December 29, 2003